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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C12Q 1/68, C12N 9/16, 15/55, C07K 14/47 — A2

(11) International Publication Number: **WO 00/05405**

(43) International Publication Date: 3 February 2000 (03.02.00)

(21) International Application Number: PCT/CA99/00646

(22) International Filing Date: 20 July 1999 (20.07.99)

(30) Priority Data:

60/093,495	20 July 1998 (20.07.98)	US
60/130,269	21 April 1999 (21.04.99)	US

(71)(72) Applicants and Inventors: SCHERER, Stephen, W. [CA/CA]; 60 Mayfield Avenue, Toronto, Ontario M6S 1K5 (CA). MINASSIAN, Berge, A. [CA/CA]; 18 Vanderhoof Avenue, Toronto, Ontario M4G 2H1 (CA). DELGADO-ESCUETA, Antonio [US/US]; 28342 Rey De Copas Lane, Malibu, CA 90265 (US). ROULEAU, Guy [CA/CA]; 4850 Cote St. Luc Road, Montreal, Quebec H3W 2H2 (CA).

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: LAFORA'S DISEASE GENE

(57) Abstract

A novel gene (EPM2A) that is deleted or mutated in people with Lafora's disease is described. The EPM2A gene encodes a protein having an active catalytic site of a protein tyrosine phosphatase. Many different sequence mutations as well as several microdeletions in EPM2A have been found that co-segregate with Lafora's disease.

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12Q 1/68, C12N 9/16, 15/55, C07K 14/47

A3

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(71)(72) Applicants and Inventors: SCHERER, Stephen, W. [CA/CA]; 60 Mayfield Avenue, Toronto, Ontario M6S 1K5 (CA). MINASSIAN, Berge, A. [CA/CA]; 18 Vanderhoof Avenue, Toronto, Ontario M4G 2H1 (CA). DELGADO-ESCUETA, Antonio [US/US]; 28342 Rey De Copas Lane, Malibu, CA 90265 (US). ROULEAU, Guy [CA/CA]; 4850 Cote St. Luc Road, Montreal, Quebec H3W 2H2 (CA).

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(88) Date of publication of the international search report:
11 May 2000 (11.05.00)

(54) Title: LAFORA'S DISEASE GENE

(57) Abstract

A novel gene (EPM2A) that is deleted or mutated in people with Lafora's disease is described. The EPM2A gene encodes a protein having an active catalytic site of a protein tyrosine phosphatase. Many different sequence mutations as well as several microdeletions in EPM2A have been found that co-segregate with Lafora's disease.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00646

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 C12N9/16 C12N15/55 C07K14/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EMBL Database Entry HS466P17 ccession number AL023806; 8 June 1998 Thorpe K.:"Human DNA sequence from clone 466P17 on chromosome 6q24: Contains a putative novel gene, the 5' part of the EPM2A (Laforin) gene...and a ca repeat polymorphism". XP002127924 see database entry ---	1-9, 17-19
P,X	MINASSIAN B ET AL: "Mutations in a gene encoding a novel protein tyrosine phosphatase cause progressive myoclonus epilepsy" NATURE GENETICS, vol. 20, no. 2, October 1998 (1998-10), pages 171-74, XP000869599 the whole document --- -/--	1-19

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2000	03/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Osborne, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 99/00646

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	SERRATOSA J ET AL: "A novel protein tyrosine phosphatase gene is mutated in progressive myoclonus epilepsy of the Lafora type (EPM2)" HUMAN MOLECULAR GENETICS, vol. 8, no. 2, February 1999 (1999-02), pages 345-52, XP000867126 the whole document	1-19
A	MINASSIAN B ET AL : "Progesss towards the positional cloning of a gene for Lafora's disease" NEUROLOGY , vol. 48, no. 3 suppl 2, 12 - 19 April 1997, page A428 XP000866505 see abstract P06.091	1-19
A	SAINZ J ET AL: "Lofora's progressive myoclonus epilepsy : narrowing the chromosome 6Q24 locus by recombinations and homozygosities" AMERICAN JOURNAL OF HUMAN GENETICS, vol. 61, no. 5, 1997, pages 1205-09, XP000866531 figure 1	1-19

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

PATENT COOPERATION TREATY

PCT

16

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
9962-9		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00646	20/07/1999	20/07/1998
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant SCHERER, Stephen, W. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17/02/2000	16.08.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Tilkorn, A-C Telephone No. +49 89 2399 8688

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00646

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-37 as originally filed

Claims, No.:

1-19 as originally filed

Drawings, sheets:

1/17-17/17 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,2,4-6,10,12,15,17,18
	No:	Claims	3,7-9,11,13,14,16,19
Inventive step (IS)	Yes:	Claims	1,4-6,17
	No:	Claims	2,3,7-16,18,19
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	-

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section I:

The applicant's attention is drawn to the fact, that the sequence listing received on 22.11.1999 with the letter of 19.11.1999 shall not form part of the international application (Rule 13ter.1(f) PCT).

Section V:

The following documents are referred to in this communication:

D1: EMBL Database Entry HS466P17 Accession number AL023806; 8 June 1998
D2: NATURE GENETICS, vol. 20, no. 2, October 1998, pages 171-74
D3: HUMAN MOLECULAR GENETICS, vol. 8, no. 2, February 1999, pages 345-52

The claimed priority is not valid for **claims 2,3,7-16, 18** and **19** because the sequences in Figure 13 (SEQ ID No 1) and in Figure 14 (SEQ ID No 2) are not entirely disclosed in either of the priority documents.
Thus, for the said claims the documents D2 and D3 published after the first priority date belong to the state of the art.

1 Novelty (Art 33(2)PCT):

1.1 **Claim 3** is not novel because each of the documents D1-D3 discloses a fragment of the EPM2A gene, which will hybridize to a polynucleotide of SEQ ID No 1 under stringent conditions.

1.2 **Claim 7** is not novel in view of D2 which discloses mutations in the EPM2A gene (D2: p 173 Table 1) and a method for detecting them (D2: p 174 col 2 para 2; p 173 Table 1). Moreover, also D3 destroys the novelty of claim 7 since it discloses several mutations within the EPM2A gene (D3: p 348 Table 1). The same argument applies to **claims 8, 16** and **19**.
The C-> T change of **claim 9** and the G->A change of **claim 11** are anticipated by each of D2 and D3 (D2: Table 1: Family L6; D3: Table 1: Family F38/S109 and

F38/S109/F95).

1.3 **Claim 13** relates to the detection of a 75 kb deletion. D2 describes a deletion that encompasses about 50 kb and is thought to include the majority of the EPM2A gene (D2: p 173 Table 1 Family LD-L4). Although D2 does not explicitly disclose to which parts of the gene (which exons) this deletion corresponds, it might include exons 1 and 2 like the 75 kb deletion of the present application (application: description: p 37 Table 3). The size of the deleted fragment is estimated on the basis of electrophoresis gels; therefore, the deletion of D2 and the present claim 13 might be identical, although the given size values differ. Thus, D2 appears to take away the novelty of **claim 13** (see also item VIII 3).

1.4 **Claim 14** relates to the detection of a 25 kb deletion. According to the description this corresponds to the deletion of exon 2 (Table 3). The deletion of exon 2 is already known from D3 (D3: p 348 Table 1 Family FD; p 346 Fig. 1).

1.5 **Claim 1** is novel, because the single relevant document (D1) only discloses a nucleic acid sequence of 158 codons encoding an aminoterminal fragment of a protein tyrosine phosphatase. The same argument applies to **claims 4-6** and **17**.

1.6 **Claim 2** is novel, because none of the available documents discloses the complete sequence of SEQ ID No 1 /Figure 13. Consequently, **claim 18** relating to the protein sequence as disclosed in SEQ ID No 2 / Figure 14 is also novel.

1.7 **Claims 10** and **12** are novel, because none of the available documents describes detection of the known mutation by the determination of restriction fragment length polymorphisms (RFLP) using *HaeI* and *PstI* respectively.

1.8 **Claim 15** is novel, because none of the available documents describes the detection of the deletion mutations by the amplification using the primers JRGXBF and JRGXBR.

2 Inventive Step (Art 33(3)PCT):

2.1 For the assessment of novelty and inventive step of **claim 2** documents D1-D3

are relevant, as the claimed priority is not valid (see above).
D2 which is considered to represent the closest prior art, is distinguished from the subject-matter of claim 2 in that the EPM2A sequence of D2 lacks 188 bp at the 5' end of the gene sequence.
The problem to be solved can thus be regarded as how to provide the complete coding sequence of the EPM2A gene.
The skilled person would search a nucleotide sequence database with the sequence of D2 (Fig 4). He would find the sequence of D1 which contains the nucleotide sequence encoding the aminoterminal end (ATG codon) of the Laforin protein and has a 188 bp overlap with the nucleotide sequence of D2. The combination of the nucleotide sequences of D1 and D2 results in the nucleotide sequence according to SEQ ID No 1 /Figure 13 of claim 2. Hence, the combination of D2 and D1 renders the solution of **claim 2** obvious. As the protein sequence is derived from the underlying nucleotide sequence, also **claim 18** seems to be obvious.

2.2 **Claims 10** and **12** appear to be obvious for the following reasons:
The mutations claims 10 and 12 refer to are known (see item V 1.7 above). Also the amplification primers used in these claims are known from D2 (D2: p 174 col 2 para 2). Furthermore, the method to determine restriction fragment length polymorphism for the detection of diseases is well known in the art. Thus, it appears to be obvious for the skilled person to select an appropriate restriction endonuclease for the respective mutation in order to carry out the RFLP method.

2.3 **Claim 15** does not appear to be inventive. The detection of a deletion in the EPM2A gene by the presence of absence of a PCR product is known from D3 (D3: Fig 1). Moreover, the deletion of exon 2 is also known from D3 (see item V 1.4) The primers used are known from D2 (D2: p 174 col 2 para 2). The general method is commonplace in the art.

2.4 As the claimed priority is valid for **claim 1,** only document D1 is relevant for the assessment of inventive step.
D1, which is considered to represent the closest prior art, is distinguished from the subject-matter of claim 1 in that D1 discloses a 5' part of the EPM2A gene within a large sequence comprising 149963 bp. In a 200 bp overlap of the sequences

99,5% identity is found.
The problem to be solved by claim 1 can be regarded as identifying functional genes within the 149963 bp.
D1 discloses a large sequence comprising a 200 bp fragment of the EPM2A gene. This part does not contain the consensus sequence of the protein tyrosine phosphatases. Hence, the skilled person was not able to identify the 200 bp fragment as encoding a protein tyrosine phosphatase and consequently he would also not have been able to establish a connection between this sequence fragment and Lafora's disease. Thus, the sequence of D1 does not render **claim 1** obvious. For the same reasons also **claims 4-6** and **17** appear to be inventive.

Section VII:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 are not mentioned in the description, nor are these documents identified therein.

The expression "incorporated herein by reference" in respect of prior art documents (e.g. page 14 para 5 and page 31 para 3) leads to a doubt as to whether the requirement of the description being self-contained is satisfied (Guidelines II, 4.17).

The sentence on page 31 l 8-10 should be deleted as it contains general statements which imply that the extent of protection may be expanded in some vague and not precisely defined way (Guidelines III 4.3a).

Section VIII:

1. **Claim 1** does not satisfy Art 6 PCT, because its scope is not clearly defined. The contribution of the present application to the art consists in the association of the gene sequence as disclosed in SEQ ID No 1 /Figure 13 in connection with Lafora's disease. Claim 1 does not include the sequence but generally relates to a protein tyrosine phosphatase. In view of the fact that protein tyrosine phosphatases are known in the art it is an undue burden for the skilled person carrying out the present invention to identify a protein tyrosine phosphatase which is associated with Lafora's disease. Thus, the nucleotide sequence encoding the

protein tyrosine phosphatase (Figure 4a or Figure 7) should have been introduced in claim 1. The same argument applies to **claim 17** in which the protein sequence of the protein tyrosine phosphatase (Figure 4a) should have been introduced respectively.

2. **Claims 4** and **5** do not meet the requirement of conciseness because they apparently relate to the same nucleotide sequence (Art 6 PCT).

3. The scope of **claims 13** and **14** is not clearly defined as required by Art 6 PCT. The size of the deleted fragment (75 kb and 25 kb respectively) does not sufficiently and unambiguously characterize the deletion and should therefore be replaced by the underlying technical feature namely the deletion of exons 1 and 2 (claim 13) and the deletion of exon 2 (claim 14) respectively (Guidelines III 4.7a).

4. **Claim 16** does not comply with Art 6 PCT, because the claim does not explicitly contain all the technical features. The reference to a table in the description should have been avoided (Guidelines III 4.10).

5. The reference to Fig 4A should have been changed to Fig 4a throughout the claims.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 22 March 2000 (22.03.00)	
International application No. PCT/CA99/00646	**Applicant's or agent's file reference** 9962-9
International filing date (day/month/year) 20 July 1999 (20.07.99)	**Priority date** (day/month/year) 20 July 1998 (20.07.98)
Applicant SCHERER, Stephen, W. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

17 February 2000 (17.02.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia RANAIVOJAONA
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

M.H

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
9962-9		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 99/ 00646	20/07/1999	20/07/1998
Applicant		
SCHERER, Stephen, W. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[X] furnished subsequently to this Authority in written form.

[X] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

[redacted] International Application No [redacted]/CA 99/00646

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 C12N9/16 C12N15/55 C07K14/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EMBL Database Entry HS466P17 ccession number AL023806; 8 June 1998 Thorpe K.:"Human DNA sequence from clone 466P17 on chromosome 6q24: Contains a putative novel gene, the 5' part of the EPM2A (Laforin) gene...and a ca repeat polymorphism". XP002127924 see database entry ---	1-9, 17-19
P,X	MINASSIAN B ET AL: "Mutations in a gene encoding a novel protein tyrosine phosphatase cause progressive myoclonus epilepsy" NATURE GENETICS, vol. 20, no. 2, October 1998 (1998-10), pages 171-74, XP000869599 the whole document --- -/--	1-19

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2000	03/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Osborne, H

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

[redacted] International Application No
[redacted]T/CA 99/00646

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	SERRATOSA J ET AL: "A novel protein tyrosine phosphatase gene is mutated in progressive myoclonus epilepsy of the Lafora type (EPM2)" HUMAN MOLECULAR GENETICS, vol. 8, no. 2, February 1999 (1999-02), pages 345-52, XP000867126 the whole document	1-19
A	MINASSIAN B ET AL : "Progesss towards the positional cloning of a gene for Lafora's disease" NEUROLOGY , vol. 48, no. 3 suppl 2, 12 - 19 April 1997, page A428 XP000866505 see abstract P06.091	1-19
A	SAINZ J ET AL: "Lofora's progressive myoclonus epilepsy : narrowing the chromosome 6Q24 locus by recombinations and homozygosities" AMERICAN JOURNAL OF HUMAN GENETICS, vol. 61, no. 5, 1997, pages 1205-09, XP000866531 figure 1	1-19

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